Manifestations of Hereditary Multiple Exostoses

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Abstract

The solitary osteochondroma, a common pediatric bone tumor, is a cartilage-capped exostosis. Hereditary multiple exostosis is an autosomal dominant disorder manifested by the presence of multiple osteochondromas. Linkage analysis has implicated mutations in the EXT *gene family, resulting in an error in the regulation of normal chondrocyte proliferation and maturation that leads to abnormal bone growth. Although exostoses are benign lesions, they are often associated with characteristic progressive skeletal deformities and may cause clinical symptoms. The most common deformities include short stature, limb-length discrepancies, valgus deformities of the knee and ankle, asymmetry of the pectoral and pelvic girdles, bowing of the radius with ulnar deviation of the wrist, and subluxation of the radiocapitellar joint. For certain deformities, surgery can prevent progression and provide correction. Patients with hereditary multiple exostosis have a slight risk of sarcomatous transformation of the cartilaginous portion of the exostosis.*

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Osteochondromas are common bone tumors seen in children and adolescents. These tumors consist of cartilage-capped exostoses found primarily at the metaphyses of the most rapidly growing ends of long bones.[1,2] Most patients have only a solitary lesion, but others may have hereditary multiple exostoses (HME), an autosomal dominant disorder manifested by multiple lesions that are more frequently associated with characteristic skeletal deformities.

The first description of a patient with multiple exostoses is attributed to Hunter in his 1786 *Lectures on the Principles of Surgery.*[3] In 1814, Boyer published the first description of a family with HME, followed by Guy's description of a second family in 1825.[4-7] By the late 1800s, most of the clinical aspects of the disease had been described.[5] Ehrenfried introduced HME into the American literature in 1915,[5] and, in 1943, Jaffe[8] made a significant contribution by further elucidating the pathology of HME and helping to differentiate the disorder from Ollier's disease (multiple enchondromatosis).

The term "multiple exostoses" was given to the condition by Virchow in 1876.[6] Numerous synonyms have been used for this disorder, including osteochondromatosis, multiple hereditary osteochondromata, multiple congenital osteochondromata, diaphyseal aclasis, chondral osteogenic dysplasia of direction, chondral osteoma, deforming chondrodysplasia, dyschondroplasia, exostosing disease, exostotic dysplasia, hereditary deforming chondrodysplasia, multiple osteomatoses, and osteogenic disease.[6]

Epidemiology

The true prevalence of HME is unknown because patients with mild multiple asymptomatic lesions may not be diagnosed. The estimated prevalence of HME in Caucasians, the most thoroughly studied population, is 0.9 to 2 individuals per 100,000.[6,9-11] Appreciably higher prevalences of between 100 and 1,310 per 100,000 have been identified in isolated populations, such as the Chamorros (Guam) and the Ojibway Indian community of Pauingassi (Manitoba, Canada), respectively.[1,12]

Pathophysiology

HME is an inherited autosomal dominant disorder with usually full penetrance.[13] Although early studies of HME populations indicated higher prevalence among males, more recent studies of nuclear families demonstrate no evidence of gender predominance.[14,15] Linkage analysis has identified two genes most strongly as-

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sociated with HME: *EXT1* on 8q24.1 and *EXT2* on 11p13.[16] Mutations in *EXT1* and *EXT2* account for approximately one half and one third of HME cases, respectively.[6,7,9,11,17] Multiple exostoses also are a distinguishing feature of Langer-Giedion syndrome (trichorhinophalangeal syndrome type II), which is caused by a deletion of both *EXT1* and the adjacent *TRPS1* gene.

EXT1 is ubiquitously expressed in many different tissues throughout the body, but the effects of *EXT1* mutations seem to be limited to growing bone.[6] The localized foci of osteochondromas in a heterozygous individual are thought to be caused by either sporadic loss of heterozygosity because of inactivation of the remaining normal allele of *EXT1* or *EXT2*, or by a second corresponding mutation outside the *EXT1* and *EXT2* loci.[18] *EXT1* and *EXT2* previously were thought to act as tumor-suppressor genes coding for proteins that inhibit abnormal cell transformation. Recent evidence suggests, however, that they instead regulate chondrocyte maturation and differentiation necessary for normal endochondral ossification within the growth plate. The molecules encoded by *EXT1* and *EXT2* are endoplasmic reticulum–resident type II transmembrane glycoproteins.[19] These glycoproteins are involved in the regulation of cell-surface heparan sulfate proteoglycans (HSPGs) that, in turn, are integral to the diffusion of several families of cell-signaling molecules.[19]

According to recent models, a complex paracrine feedback loop exists within the growth plate in which local molecular signaling controls the rate of chondrocyte proliferation and differentiation.[19] Normal prehypertrophic chondrocytes in the growth plate produce Indian hedgehog (Ihh), a signaling molecule that stimulates chondrocyte proliferation upon binding to osteogenic cells in the metaphyseal perichondrium. Ihh binding by these cells signals the upregulation of a second signaling molecule, parathyroid hormone–related peptide (PTHrP). PTHrP then binds to proliferating and prehypertrophic chondrocytes and postpones cell differentiation and apoptosis. This negative feedback loop favors normal longitudinal cartilage growth and persists until decreased expression of Ihh or PTHrP disrupts the equilibrium, leading to chondrocyte apoptosis and resulting ossification. EXT proteins are thought to synthesize HSPGs, which are necessary for the normal diffusion and/or signaling by Ihh in the growth plate (Fig. 1). Thus, HME may be explained by a defect in HSPG biosynthesis that causes a local error in the normal negative feedback loop regulating chondrocyte proliferation and maturation that, consequently, results in premature differentiation and abnormal bone growth at the growth plate.[19,20]

HSPGs produced by EXT proteins also have been implicated as coreceptors for fibroblast growth factor (FGF), which regulates endochondral bone development. Abnormalities in FGF signaling are responsible for a number of skeletal dysplasias, includ-

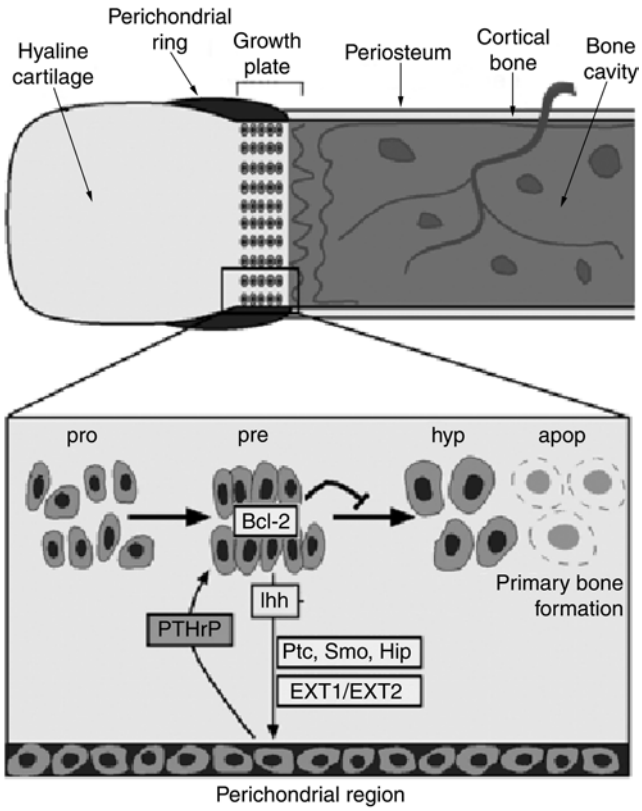

Figure 1 The growth plate during endochondral bone formation. Prehypertrophic chondrocytes (pre) localized within the growth plate produce Indian hedgehog (Ihh), a cell-signaling molecule, which diffuses to the receiving cells via heparan sulfate proteoglycans that are glycosylated by *EXT1* and *EXT2*. Ihh binding induces chondrocyte proliferation by upregulating a second signaling molecule, parathyroid hormone–related peptide (PTHrP). PTHrP binds to the parathyroid/PTHrP receptor on a subpopulation of proliferating (pro) and prehypertrophic chondrocytes, thereby inducing production of an antiapoptotic protein. In the absence of negative feedback, chondrocytes differentiate into hypertrophic chondrocytes (hyp), which undergo apoptosis (apop) before being replaced by bone-forming osteoblasts. (Reproduced with permission from Duncan G, McCormick C, Tufaro F: The link between heparan sulfate and hereditary bone disease: Finding a function for the EXT family of putative tumor suppressor proteins. *J Clin Invest* 2001;108:511-516.)

ing achondroplasia, hypochondroplasia, and thanatophoric dysplasia. Mutations in *EXT1* and *EXT2* may impair HSPG synthesis, leading to diminished FGF signaling and abnormal chondrocyte proliferation at sites of exostosis formation.[16] More research is required to fully elucidate the mechanism behind exostosis formation in HME.

Clinical Presentation

Patients with HME have multiple cartilage-capped exostoses that may be sessile or pedunculated (Fig. 2). Sessile exostoses are broad-based and characterized by a diameter that is greatest at the base contiguous with the cortex, whereas pedunculated lesions are marked by a diameter that increases following a tapered stalk. Although usually located at the most rapidly growing ends of long bones, the lesions also are frequently found in the vertebral borders of the scapulae, ribs, and iliac crests. Osteochondromas have been observed in the tarsal and carpal bones; however, they are seldom apparent clinically. There is only one reported case of an exostosis of the skull and no reported cases of a lesion arising from the facial bones,[6,8] likely as a result of intramembranous ossification at these locations.

Exostoses are initially diagnosed in the first decade of life in more than 80% of individuals with HME.[21] They are commonly first discovered on the tibia or scapula because those are often the most conspicuous locations. HME occasionally is diagnosed at birth, but such an early diagnosis is usually the result of a specific search in the presence of a positive family history. The size and number of lesions vary considerably between affected individuals, and patients with smaller and fewer lesions may never become symptomatic. The lesions tend to enlarge while the physes are open at a growth rate proportionate to the overall growth of the patient; cessation of growth usually occurs at skeletal maturity. Lesions have been infrequently reported to spontaneously regress during the course of childhood and puberty. Recurrence of an exostosis after surgical excision, although rare, may be attributed to incomplete removal of lesions contiguous with the physis in growing children or to incomplete removal of the cartilaginous cap.[6,22]

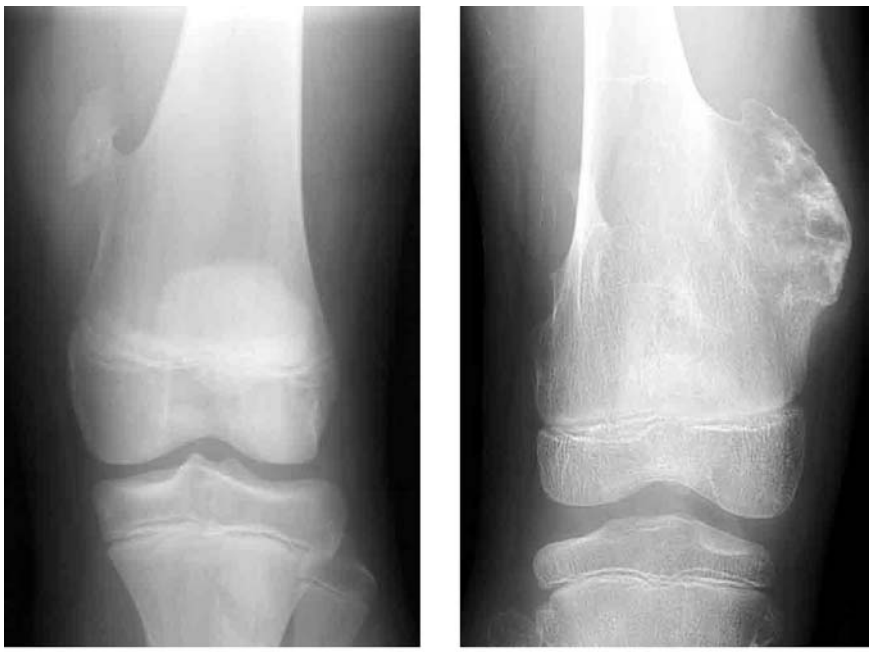

Figure 2 **A,** Anteroposterior radiograph of a pedunculated osteochondroma. **B,** Anteroposterior radiograph of a sessile osteochondroma.

Clinical Manifestations

Although exostoses are histologically benign lesions, they can cause a variety of clinical problems. Patients with HME most frequently report pain and cosmetic concerns. Pain may be the result of a variety of problems associated with the exostoses, such as a bursa formation or repeated soft-tissue trauma over a prominent osteochondroma. In pedunculated osteochondromas, fracture at the base may occur after local trauma. Finally, pain associated with snapping or popping may occur when a large muscle repeatedly moves over the top of an exostosis (eg, quadriceps over a distal femoral exostosis during running). Restricted range of motion (ROM) is a common report of individuals with severe involvement of the proximal femur or forearm.

Associated soft-tissue problems include impingement, entrapment, or injury of tendons, nerves, or vessels. Spinal involvement has been documented in 7% of affected patients; spinal cord compression is a rare but well-documented complication of HME.[23] Both urinary and intestinal obstruction, although uncommon, have been reported as complications of the presence of osteochondroma. Dysphagia secondary to a ventral cervical exostosis and spontaneous hemothorax as a result of rib exostoses has been described.[24,25] Exostoses also have been noted to interfere with normal birth, leading to a higher rate of cesarean sections.[9]

The most common deformities associated with HME include short stature, limb-length discrepancies, valgus deformities of the knee and ankle, and asymmetry of either the pectoral or pelvic girdles. Osteochondromas in the forearm can result in shortening of the ulna with resultant bowing of the radius with ulnar deviation of the wrist, subluxation of the carpus on the distal radius, and subluxation or dislocation of the radial head[9,11,15] (Fig. 3). Less commonly, relative shortening and angular deformities of the metatarsals, metacarpals, and phalanges, as well as scoliosis, coxa valga, and acetabular dysplasia, have been described.[14,15,26,27]

Patients with HME are frequently of short stature, with most heights 0.5 to 1.0 SD below the mean.[3,15] Affected men and women have heights below the fifth percentile in 36.8% and 44.2% of cases, respectively.[9] Sitting height is generally less affected than total height, indicating more extensive involvement of the limbs than of the axial skeleton.[15]

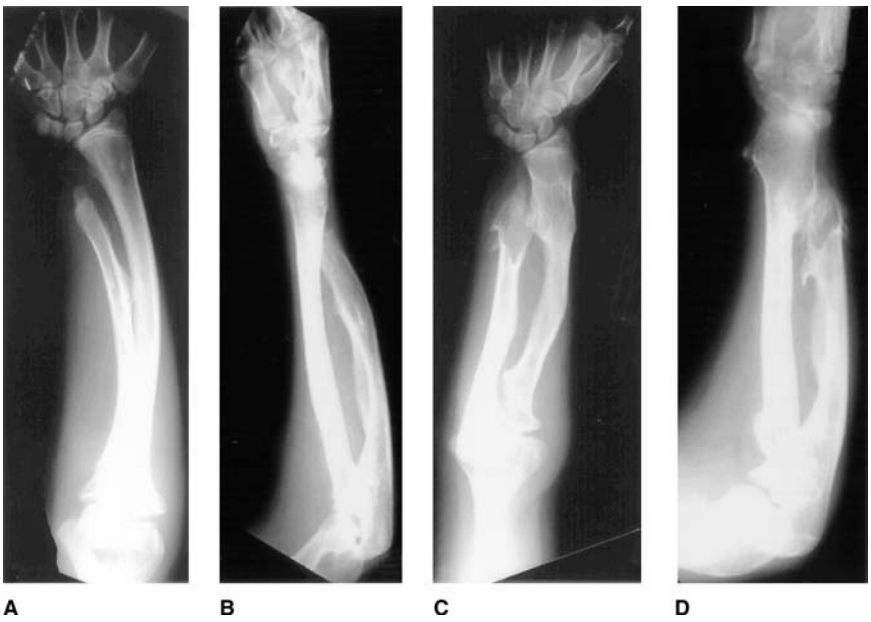

Figure 3 Anteroposterior **(A)** and lateral **(B)** radiographs of the right forearm of a 15-year-old boy with hereditary multiple exostoses demonstrating multiple exostoses, ulnar shortening, and ulnar carpal drift. Anteroposterior **(C)** and lateral **(D)** radiographs demonstrating similar deformities in the left forearm of the same boy. (Reproduced with permission from Pierz KA, Stieber JR, Kusumi K, Dormans JP: Hereditary multiple exostoses: One center's experience and review of etiology. *Clin Orthop* 2002;401:49-59.)

Upper Extremity Involvement

Forearm

Osteochondromas of the upper extremities commonly cause forearm deformities. The prevalence of such deformities is as high as 40% to 74%.[7,8,11,15,28] Disproportionate ulnar shortening has been frequently described and may be associated with radial bowing. Subluxation or dislocation of the radial head has been reported in 22% to 33% of patients with HME.[15,28] Dislocation of the radial head is associated with loss of pronation, enhanced ulnar variance, and functional impairment.[29] Disruption of the distal radioulnar joint, ulnar deviation, and ulnar translocation of the carpal bones are often associated with HME. This complex of deformities seems to be similar to Madelung's deformity, but it does not manifest in the characteristic relative elongation or dorsal subluxation of the distal ulna seen in Madelung's deformity.[15]

Jaffe[8] and Porter et al[17] suggested that the length of forearm bones correlates inversely with the size of the exostoses. Moreover, lesions with sessile rather than pedunculated morphology have been associated with more notable shortening and deformity.[5] Thus, the skeletal growth disturbance observed in HME is a local effect; the growth of the osteochondroma overwhelms and retards the growth of any closely associated physis, resulting in a tethering effect on paired structures. Larger lesions with greater cortical involvement tend to influence bone growth more substantially than do smaller lesions.

The disproportionate shortening of the ulna can be generally attributed to two causes. First, because the distal ulnar physis is responsible for greater longitudinal growth relative to that of the distal radius (85% versus 75%, respectively), equal involvement results in more substantial ulnar shortening. Second, bones with a smaller cross-sectional diameter tend to be shortened more considerably when affected by HME; this can be attributed to greater proportionate involvement of the physis. As a result, equal involvement of the two bones preferentially affects the ulna, which has a diameter of only one fourth that of the radius. Consequently, radial bowing was thought to be caused by a tethering effect of relative ulnar shortening.[3] Burgess and Cates,[4] however, found that radial bowing was not correlated with measured ulnar shortening in their series of 35 patients. They reported a strong correlation between ulnar shortening in excess of 8% and dislocation of the radial head.

The extent of forearm involvement in patients with HME is strongly associated with the general severity of the disease. Taniguchi[30] classified his patients into three groups: (1) those

with no involvement of the distal forearm, (2) those with involvement of the distal radius or ulna without shortening of either bone, and (3) those with involvement of the distal radius or ulna with shortening of either bone. He reported that increasing forearm involvement was associated with an earlier age of diagnosis of HME, a greater number of generalized exostoses as well as of exostoses affecting the knee, shorter stature, and increased valgus deformity of the ankle. All of the patients with dislocation of the radial head were categorized in group 3, with shortening of either bone in addition to distal exostoses.

Many of the deformities of the forearm are amenable to surgical treatment. Knowledge of the natural history of the disease and timely intervention are the keys to preventing deformity in patients with HME. Although early aggressive surgery is often recommended, it is also controversial.[4,7,31] Specific indications for surgery include painful lesions, an increasing radial articular angle, progressive ulnar shortening, excessive carpal slip, loss of pronation, and increased radial bowing with subluxation or dislocation of the radial head.[31]

Masada et al[32] classified forearm deformities into three types according to the morphology of the deformity (Fig. 4). In type I, the distal ulna has the greatest exostosis formation. The ulna is shortened with bowing of the radius, but the radial head is not affected, and the proximal part of the radius is not dislocated. Tapering of the ulnar head and ulnar tilt of the distal radius are both present. This deformity is the most common and is observed in 55% (31/56) to 61% (22/36) of forearms.[28,32] In type II, the radial head is dislocated and the ulna is shortened. Bowing of the radius is less severe than in the type I deformity, secondary to dislocation of the radial head. In type IIa, the radial head is dislocated as a result of exostosis formation at the proximal metaphysis of the radius. In type IIb, radial head dislocation occurs in the absence of a proximal radial exostosis. In type III, the primary exostosis formation is in the metaphysis of the distal radius, with relative shortening of the radius compared with the ulna.[32] Based on successful outcomes in a limited number of patients with a type I deformity, Masada et al[32] recommended exostosis excision, radial osteotomy, and immediate ulnar lengthening.

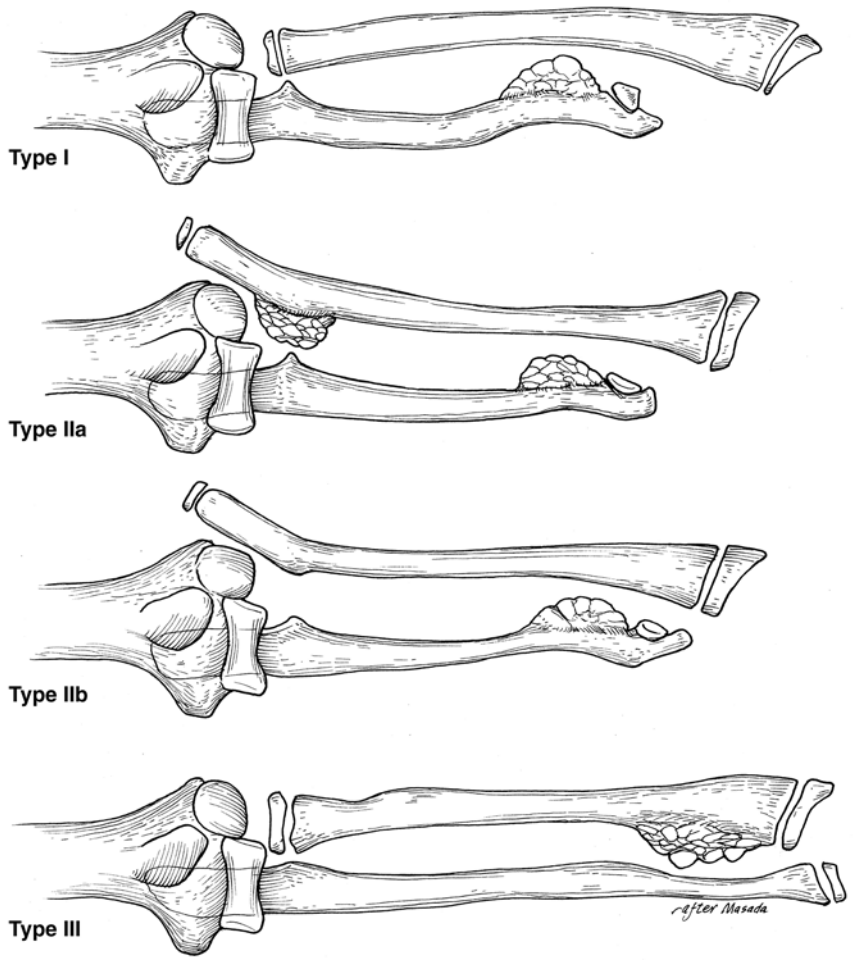

Figure 4 Masada classification of forearm deformities in hereditary multiple exostoses. Type I: Primary exostosis formation is in the distal portion of the ulna, which is relatively short compared with the radius. Type IIa: In addition to ulnar shortening, the radial head is dislocated secondary to an exostosis at the proximal metaphysis of the radius. Type IIb: The radial head is dislocated without a proximal radial exostosis. Type III: Primary exostosis formation is in the metaphysis of the distal radius, leading to relative shortening of the radius compared with the ulna. (Adapted with permission from Masada K, Tsuyuguchi Y, Kawai H, Kawabata H, Noguchi K, Ono K: Operations for forearm deformity caused by multiple osteochondromas. *J Bone Joint Surg Br* 1989;71:24-29.)

In a study of 18 patients who underwent surgery for correction of forearm deformities, Fogel et al[31] reported that, although early osteochondroma excision alone can decrease or halt the progression of forearm deformity, it does not consistently provide full correction. Ulnar translocation of the carpal bones on the distal radius can be corrected by ulnar lengthening, but persistent relative ulnar shortening is likely to recur. For patients with increased

radiocarpal angulation or carpal subluxation, osteochondroma excision in conjunction with distal radial osteotomy or hemiepiphyseal stapling resulted in improved function and cosmesis. The seven forearms that received all three procedures showed improvement in the degree of ulnar deviation. The mean improvement in the radial articular angle was 20°. The mean range of forearm rotation in the six forearms with available measurements improved from 78° preoperatively to 118° at a minimum 2-year follow-up.[31]

Pritchett[33] performed ulnar lengthening in 10 forearms, resulting in improved cosmetic appearance, ROM, and stability of the radial head. Waters et al[34] performed acute ulnar lengthening in 17 patients with HME. They used a long Z-cut osteotomy and a temporary intraoperative external fixator with long plate fixation (Fig. 5). Eleven patients additionally underwent distal radial osteotomy and achieved stable reduction of abnormal radial inclination. Of the surgically treated patients, 85% experienced improvement of pronation/supination (average increase, 39°). Forty percent had improved radial/ulnar deviation (average increase, 15°). Sixty percent had unchanged radial/ulnar deviation, but postoperatively their arc of motion improved to a more neutral alignment (average of both radial and ulnar deviation, 22°).

Complete dislocation of the radial head can be a serious sequela of forearm deformity and can result in pain, instability, and decreased motion at the elbow. Early surgical intervention should be considered. Historically, for this type II deformity in skeletally mature patients, excision of the radial head was recommended in addition to excision of exostosis, radial osteotomy, and immediate ulnar lengthening.[32] Attempts at surgical relocation of the radial head have not consistently proved to be successful.[7] Radial head position can be gradually corrected with an Ilizarov fixator to lengthen the ulna and to apply traction on the radius, either directly through the interosseous membrane or indirectly through the carpus by distal ulnar fixation or a radioulnar transfixion wire.[35] Patients may be left with a painful, stiff, or weak upper extremity despite surgical treatment.

Controversy exists concerning the necessity of early surgery and whether the outcomes are superior to those of untreated patients. Stanton and

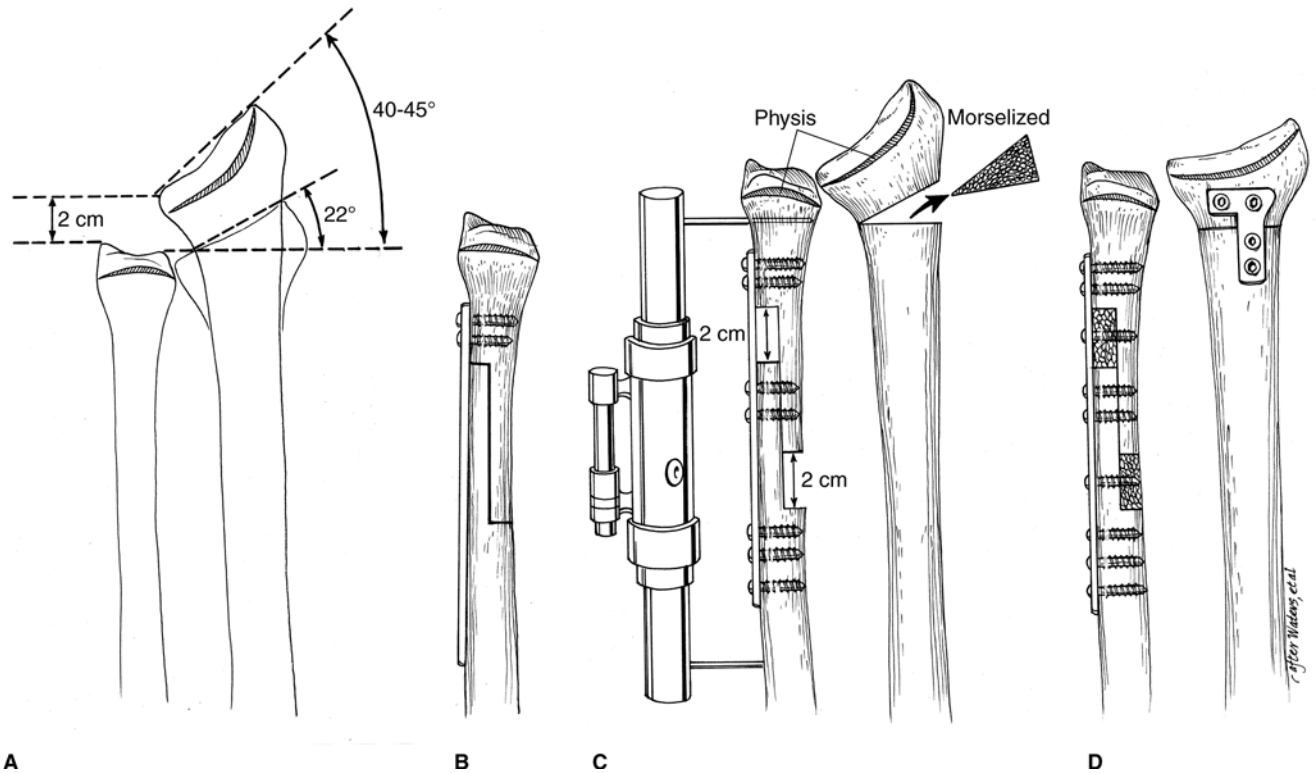

Figure 5 **A,** Indications for closing-wedge radial osteotomy to decrease radial inclination and ulnar lengthening for correction of length discrepancy. The radial osteotomy is performed first. **B,** The ulna is exposed, and the external fixator and the distal end of the plate are applied. A long Z-cut osteotomy is performed. **C,** The ulna is slowly lengthened until near-neutral ulnar variance is achieved. **D,** The plate is fixed, the external fixator is removed, and the bone graft is placed. (Adapted with permission from Waters PM, Van Heest AE, Emans J: Acute forearm lengthenings. *J Pediatr Orthop* 1997;17:444-449.)

Hansen[29] contend that deformities of the upper extremity in patients with HME are well tolerated and result in minimal functional loss when measured both subjectively and objectively. Similarly, Arms et al[36] conducted a telephone survey of 37 skeletally mature patients, who reported satisfaction with both function and cosmesis despite the presence of deformity. Noonan et al[28] reported that untreated patients tended to adapt well to their differences; only 13% reported appreciable pain or limitation related to job performance. In that study, however, 40 of 77 upper extremities were more than 2 SD below the mean in at least one area of functional assessment, including grip strength, pinch strength, ROM, and hand function. Additionally, Stanton and Hansen[29] reported a prevalence of early degenerative joint disease in 3 of 56 involved upper extremities in their cohort (average age, 21 years). Wood et al[7] noted that surgeries of the distal forearm may result in only modest functional improvement but marked cosmetic benefit.

Hand

Hand involvement has been reported in 30%[11] to 79%[21] of patients. Fogel et al[31] observed metacarpal and phalangeal involvement in approximately 70% of their patients. In their series of 63 patients, Cates and Burgess[26] reported that patients with HME fall into two groups: those with no hand involvement and those with substantial hand involvement, averaging 11.6 lesions per hand. The ulnar metacarpals and proximal phalanges were most commonly involved, with the thumb and distal phalanges affected less frequently. Although exostoses of the hand resulted in shortening of the metacarpals and phalanges, brachydactyly also was observed in the absence of exostoses. Only 4 of 22 patients with hand involvement required surgery.[26] In most reports, the majority of patients are asymptomatic.[15,26] Cates and Burgess[26] observed no angular deformities of the digits, but these have been reported. Pseudomallet finger secondary to the presence of an exostosis located on the distal second phalanx has been reported, with successful treatment after resection.[37]

Lower Extremity Involvement

Limb-length discrepancy is commonly seen in patients with HME. A clinically notable inequality ≥2 cm has been reported in 10% to 50% of affected individuals.[11,15,38] Shortening can occur in the femur and the tibia. The femur is affected approximately twice as commonly as the tibia.[15] Surgical treatment with appropriately timed epiphysiodesis has been satisfactorily performed in growing patients.

Femur

In addition to limb-length discrepancies, several lower extremity deformities have been documented. Lesions of the proximal femur have been reported in as few as 30% in some series to as many as 90% in other studies of patients with HME, with coxa valga present in up to 25% of individuals with the disorder.[11,15,21] Porter et al[39] correlated increasing osteochondroma load with an increasing femoral neck-shaft angle. Femoral anteversion and valgus have been associated with exostoses located in proximity to the lesser trochanter.[40] There have been at least nine reported cases of acetabular dysplasia in patients with HME.[27,41] Acetabular dysplasia, which is caused by exostoses located within or about the acetabulum or on the medial femoral neck, can lead to femoral lateralization. The femoral head itself does not appear to be affected. It is critically important to recognize this process early and to provide appropriate treatment. Coxa valga may require early varus osteotomy.[41]

The distal femur is variably involved in as little as 70% to as many as 98% of affected individuals; the proximal tibia ranges from 70% to 98% involvement and the fibula, from 30% to 97% of cases.[11,15,21,38] As a result, valgus knee deformities are found in 8% to 33% of patients with HME.[10,11,15,38] Patellar dislocation is another complication of valgus knee deformity in HME.[10]

Knee

Shapiro et al[15] and Nawata et al[10] suggested that valgus knee deformity was primarily caused by proximal tibia changes. In fact, both the distal femur and the proximal tibia tend to contribute to the deformity.[38] Nawata et al[10] found the fibula to be shortened disproportionately compared with the tibia and contended that the disparity was responsible for the consistent valgus direction of the deformity. In the series by Shapiro et al,[15] 7 of 20 patients with this valgus deformity required corrective osteotomy. In another series, 3 of 13 knees required treatment, including femoral opening wedge osteotomy, proximal tibial hemiepiphysiodesis, and high tibial osteotomy[38] (Fig. 6). In the same series, 7 of 31 knees had opposing angular deformities of the distal femur and proximal tibia, which compensated to produce acceptable knee alignment. These changes were not clinically apparent on physical examination because the normal mechanical axis was maintained by complementary lateral distal femoral angles and medial proximal tibial angles. It is unclear whether patients with this abnormality in knee geometry are predisposed to degenerative joint disease.[38]

Ankle

Exostoses about the ankle can affect the growth of the extremity and may cause pain, decreased ROM, weakness, and deformity. Valgus deformity of the ankle is common in patients with HME and is observed in approximately half of affected patients.[3,14,15,38] The deformity can be at-

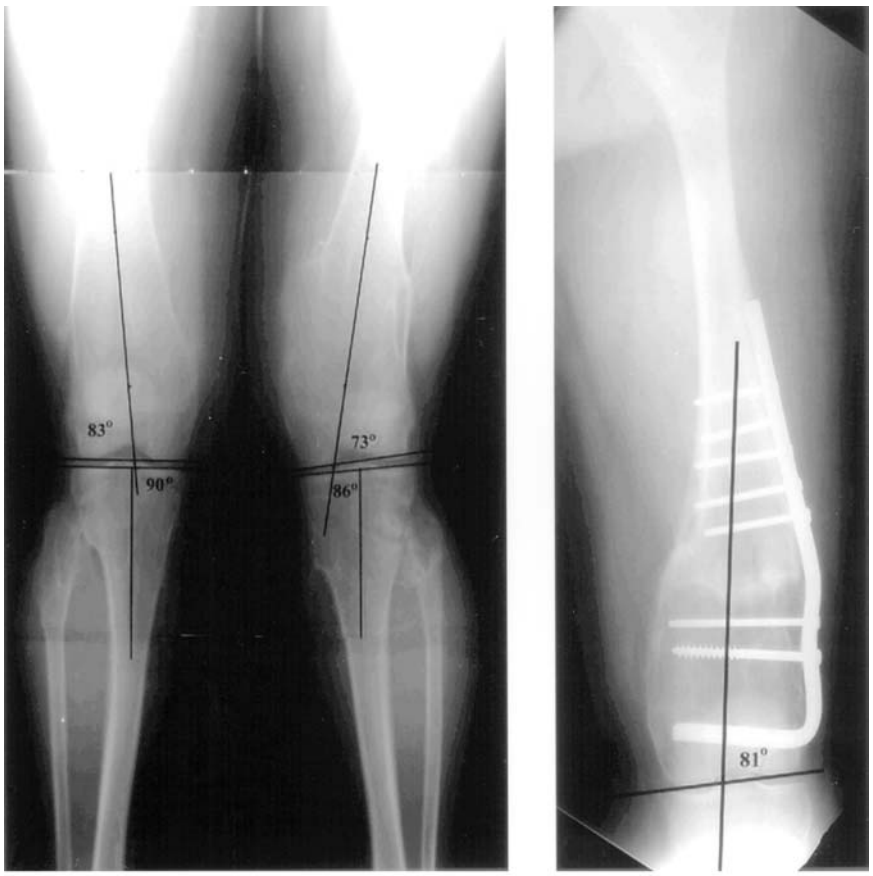

Figure 6 **A,** Standing anteroposterior radiograph of the lower extremity of a 16-year-old girl demonstrating multiple exostoses and a left femoral valgus deformity. **B,** Anteroposterior radiograph 6 months postoperatively of a left distal femur with the valgus deformity corrected by an opening wedge femoral osteotomy. (Reproduced with permission from Pierz KA, Stieber JR, Kusumi K, Dormans JP: Hereditary multiple exostoses: One center's experience and review of etiology. *Clin Orthop* 2002;401:49-59.)

tributed to multiple factors, including shortening of the fibula relative to the tibia. Resulting obliquity of the distal tibial epiphysis and medial subluxation of the talus also can be associated with this deformity. Partial compensation may be provided by a developmental obliquity of the superior talar articular surface.[15] In one series of 23 adolescents, exostoses of the distal tibia were more commonly symptomatic than those of the distal fibula.[22] Lesions in the ankle most often became symptomatic in the second decade of life. Noonan et al[42] found signs of early osteoarthritis in 14 of 75 ankles in their cohort of untreated adults (average age, 42 years). Seventy percent of patients with ankle involvement reported impairment secondary to decreased ROM.

Patients with smaller, asymptomatic lesions of the distal tibia and fibula can be treated nonsurgically and followed with serial radiographs until skeletal maturity.[22] Chin et al[22] recommend excision of symptomatic lesions in skeletally mature patients as well as in skeletally immature patients who fail nonsurgical treatment. Patients with substantial remaining growth tend to experience progressive deformation; thus, partial or complete resection with preservation of the epiphysis may be appropriate. An oblique osteotomy of the distal fibula permits optimal exposure of the tibial exostosis and allows more complete resection.[22]

In more advanced cases, excision of exostoses alone does not correct the ankle deformity, although it may improve preoperative symptoms and cosmesis.[22,43] Medial hemiepiphyseal stapling of the tibia in conjunction with excision of the exostoses performed with early ankle deformity can correct a valgus angle ≥15° associated with limited shortening of the fibula.[15,43] Fibular lengthening has been used effectively for severe valgus deformity with more significant fibular shortening (ie, when the distal fibular physis is located proximal to the distal tibial physis).[43] Supramalleolar osteotomy of the tibia as well as osteotomy and placement of an Ilizarov device also have been used effectively to treat severe valgus ankle deformity.[15,43] In skeletally immature patients, hemiepiphysiodesis or fixation with a transphyseal screw may allow for correction[38] (Fig. 7). Such a procedure is indicated when there is a symptomatic or progressive deformity with sufficient remaining growth to allow for adequate correction. Growth of exostoses also can result in tibiofibular diastasis, which can be treated by early excision of the lesions.

Neurologic and Vascular Complications

HME can cause both neurologic and vascular problems throughout the extremities. Wicklund et al[9] reported peripheral nerve compression symptoms in 22.6% of the 180 patients in their series. Lesions arising from the medial aspect of the proximal humeral physis are often symptomatic because several important neurovascular structures may encounter compression there. Peroneal neuropathy associated with exostoses of the proximal fib-

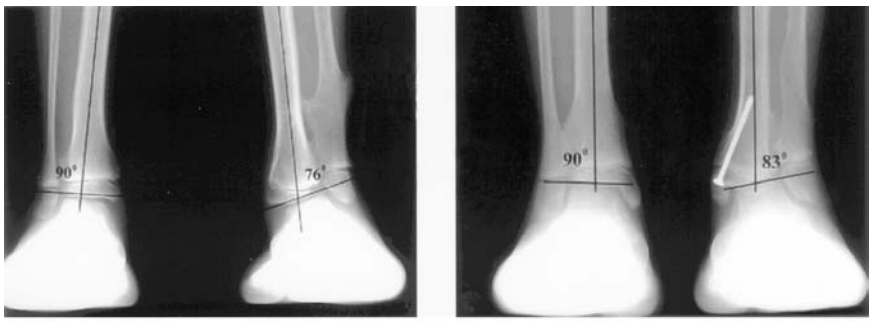

Figure 7 **A,** Standing anteroposterior radiograph of the ankles of a 7-year-old girl demonstrating left ankle valgus. **B,** Standing anteroposterior radiograph taken 34 months after surgery. Treatment with a medial transphyseal screw allowed for continued lateral growth to correct the deformity. (Reproduced with permission from Pierz KA, Stieber JR, Kusumi K, Dormans JP: Hereditary multiple exostoses: One center's experience and review of etiology. *Clin Orthop* 2002;401:49-59.)

ula in children is a recognized complication. Cardelia et al[44] described the "heel walking extinction test" as being helpful in diagnosing peroneal nerve injury. In this test, the patient is asked to ambulate to fatigue on his or her heels with both ankles in dorsiflexion to determine whether the involved side has a lower threshold for fatigue.

The prevalence of vascular compression secondary to exostoses has been reported to be as high as 11.3%.[9] In a series of 97 cases of vascular complications stemming from osteochondromas, 71 were from sporadic osteochondromas, and 26 were associated with HME.[45] Pseudoaneurysm, vascular compression, arterial thrombosis, aneurysm, and venous thrombosis were the most commonly reported complications. Claudication, acute ischemia, and phlebitis were the most commonly associated clinical presentations. Eighty-three percent of vascular problems were located in the lower extremity, with the popliteal artery most frequently involved.[45]

To address symptomatic neurovascular involvement, exostosis excision should be performed along with direct nerve or vessel decompression. Neurovascular structures are not necessarily stretched and pushed aside by a lesion, but they may be either attenuated over the surface or intimately wrapped around the base of an exostosis. Knowledge of the relevant anatomy, adequate exposure, and thorough preoperative planning can facilitate successful surgical treatment.

Malignant Transformation

Malignant transformation of a benign osteochondroma into a chondrosarcoma is another complication of HME. Fortunately, many of the chondrosarcomas in this setting are low grade and can be treated successfully with wide excision. Patients with such lesions usually present with an expanding painful mass. Rarely, nerve compression is the presenting complaint. Ochsner[46] reported on 59 patients with HME who had malignant transformation. The mean age at diagnosis of malignancy was 31 years, with malignant degeneration seldom occurring in the first decade or after the fifth decade of life. The reported incidence of malignant degeneration is highly variable, ranging from 0.5% to 25%.[40,47] This disparity can be attributed not only to a possible selection bias inherent for a tertiary referral center but also to the inability to detect all HME patients without malignant degeneration, thus making it difficult to determine the true denominator.[5] More recent studies indicate that the rate of secondary malignancy is <5% per patient.[1,11,40,48] The risk of malignant transformation may vary among families, reflecting genetic heterogeneity predisposing to malignant degeneration.[11] In their cohort of 217 individuals in 42 French families affected with HME, Francannet et al[49] observed chondrosarcomas in 9 patients, all of which were associated with *EXT1* mutations.

Because of this risk, patients with HME should be followed carefully to detect early sarcomatous transformation. Continuous growth of a lesion after skeletal maturity should raise the suspicion of malignancy, especially when accompanied by pain. Additionally, in adults, the presence of an osteochondroma with a cartilaginous cap >2 cm has been associated with an increased chance of malignancy.[2] Ultrasound is effective for measuring cap thickness on superficial lesions, but magnetic resonance imaging may be better for evaluating more deeply located lesions. Ideally, skeletally mature patients should be followed by an orthopaedic oncologist. Appropriate patient education is crucial for early identification of high-risk lesions.

Summary

HME is an autosomal dominant disorder manifested by multiple lesions that are frequently associated with characteristic skeletal deformities. Linkage analysis has identified two genes associated with HME: *EXT1* and *EXT2*. The molecules encoded by *EXT1* and *EXT2* are endoplasmic reticulum–resident type II transmembrane glycoproteins that are integral to HSPG biosynthesis. Mutation of the *EXT1* or *EXT2* gene causes an error in the regulation of normal chon-

drocyte proliferation and maturation that results in abnormal bone growth.[19,20] Although exostoses are benign lesions, they often lead to clinical problems. The most common deformities seen in HME include short stature, limb-length discrepancies, valgus deformities of the knee and ankle, asymmetry of the pectoral and pelvic girdles, bowing of the radius with ulnar deviation of the wrist, and subluxation of the radial head.[9,11,21] For certain characteristic deformities, surgical treatment can prevent progression and provide correction.

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